A STUDY OF FAVIPIRAVIR IN HOSPITALIZED COVID-19 PATIENTS, EXPERIENCE FROM A SINGLETERTIARY CARE CENTRE

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Abstract:

Background: Various therapeutic modalities are under evaluation for the COVID-19 pandemic which has gripped the world, India being badly affected. Favipiravir is one of the newer antivirals approved by DCGI for use in COVID-19 pneumonia in June 2020. Our study aims to evaluate its efficacy and safety profile. **Methods:** Ours is a retrospective observational study involving patients given favipiravir as per protocol in June. A historical cohort of patients admitted in April through May was used for comparison. **Results:** A total of 69 patients were studied in the favipiravir arm as compared to 400 in the Standard of Care group. 65 (94.20%) patients given favipiravir tested negative by the 10th day whereas in the SOC group, 224 (56%)patients out of 400 tested negative. 17 (24.64%) patients given favipiravir were on oxygen support which reduced to 0 (0%) on day 10, where as in the SOC group, 49 (12.25%) patients were on oxygen support initially which increased to 54 (13.5%). 12 (17.39%) patients administered favipiravir developed mild transaminits and 3 (4.35%) patients developed diarrhoea. **Conclusion:** Favipiravir is effective in mild to moderate COVID-19 pneumonia for enhancing viral clearance and resulted in clinical improvement.

Keywords: Adverse Effects, Antivirals, Clinical Improvement, COVID-19, Favipiravir, Viral Clearance

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Introduction:

COVID-19 respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly become a global health issue since it emerged in December 2019[1]. SARS-CoV-2 is a single-stranded RNA beta-coronavirus encoding an RNA-dependent RNA polymerase (RdRp) and proteases. Both RdRp and viral proteases are considered important targets for potentially therapeutic antiviral agents[2].Various antiviral treatment modalities are under

evaluation at present across the globe like remdesivir, darunavir, lopinavir/ritonavir, etc[3].

Favipiravir(T-705) a purine nucleic acid analog, is a broad-spectrum oral antiviral agent that inhibits the RdRp of RNA viruses[4].A few studies have demonstrated it to show in vitro activity against many RNA viruses, including arenaviruses, bunyaviruses, flaviviruses, Ebola virus, and influenza virus, as well as SARS-CoV-2[5].

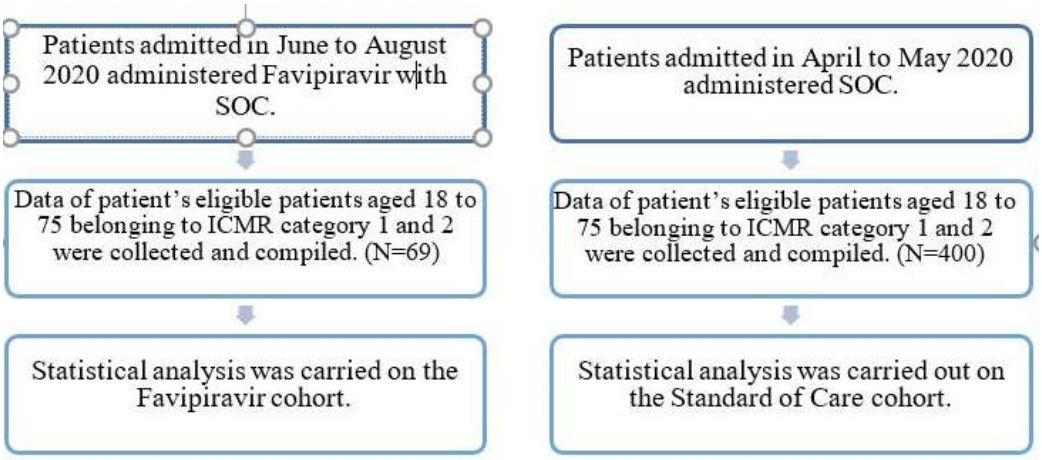
In India, the DCGI (Drug Controller General of India) approved this drug for emergency use in June 2020 for its use in mild to moderate cases of COVID-19 and was included in certain state and institutional guidelines[6]. The state and district administrations procured this drug for the benefit of patients and it was made available at our institute as well. As per recommendation, favipiravir was administered in a dose of 1800 mg twice a day on day 1 followed by 800 mg twice a day from day 2 to day 7 in non-pregnant patients from 18 to 75 years of age having mild to moderate illness as per Indian Council of Medical Research and Ministry of Health and Family Welfare[6] (mild cases are the patients presenting with fever and/or upper respiratory tract illness (Influenza Like Illness, ILI), without pneumonia and moderate cases are the patients presenting with Pneumonia, Respiratory Rate of 24 to 30/minute and/or oxygen saturation (SpO2) 90%-94% on room air)[7].

Despite the widespread usage of this drug, there are still very limited studies available evaluating its efficacy, especially in the South Asian Population and hence this retrospective study was undertaken.

Material and Methods

Study Design: Ours is a retrospective, single center study. The data of patients who were administered favipiravir (June to August 2020) at our institute was extracted and evaluated and compared with a similar historic cohort of patients administered the prevailing standard of care (SOC) as per Indian Council of Medical Research (ICMR) guidelines before the introduction of favipiravir , that is in the months of April through May. (Figure 1)

Figure 1: Study Design



*(SOC: Standard of Care)

The study was approved by the Institutional Review Board [NHL IRB 19/10/2020]. The need for consent was waived off due to the nature of the study.

Eligibility Criteria: COVID-19 positive patients (by Rapid Antigen (RAT) and Real Time Polymerase Chain Reaction (RT PCR) between the ages of 18-75 years of age who were suffering from mild to moderate COVID-19 illness as per) and were given favipiravir along with SOC between June, 2020 to August, 2020 as per protocol and no other experimental therapy (convalescent plasma, remdesivir, tocilizumab) were included in our study.

Efficacy Measures: The efficacy of treatment was evaluated by time of viral clearance and wean off from oxygen. The repeat viral sampling in both groups was done by oropharyngeal and nasopharyngeal swab RT-PCR (Quantstudio 5®) at the institutional laboratory which was authorized to carry out the tests by the government.

Statistical Analysis: The quantitative data were described as the mean ± standard deviation, or as the median (interquartile range (IQR)). The qualitative data were described by number of cases (proportion, %). Patient characteristics were compared Fisher's exact test for categorical data, and the Student's *t*-test and ANOVA for continuous data. All analysis was done using Microsoft Excel 2017 ® and IBM SPSS ®(Version 25) software. A *p* value lower than 0.05 was considered as statistically significant.

Results

Patients and Baseline Analysis:

The data of eligible COVID-19 patients aged from 18 to 75 who were administered favipiravir in the months of June to August 2020 was collected and compiled. A record of 74 patients was found. 5 patients were excluded due to the drug being withdrawn midway through treatment or the patient being transferred to another center

A total data of 400 patients belonging to the same clinical group and ICMR category admitted to our institute in the months of April and May 2020 and administered only SOC was taken as the comparator group. The baseline demographics and characteristics of patients in both the groups are listed in Table 1.

Table 1: Baseline Characteristics

Parameter	Favipiravir (n=69)	SOC (N=400)	P value
Age	48.14±13.99	44.98±15.94	0.1226
Days since symptom onset (IQR)	4(2-4)	4(2-6)	0.0201
Male	49(71.01%)	236(59%)	0.0626
Comorbidites	34(49.28%)	127(31.75%)	0.0059
On Oxygen	17(24.64%)	49(12.25%)	0.0133

*SOC: Standard ofCare

IQR: Inter Quartile Range

The mean age of the favipiravir treated group was 48.14±13.99 compared with 44.98±15.94 for the SOC group, the difference being statistically insignificant (*p=0.1226.*). 49(71.01%) of patients in favipiravir group were male compared to 236(59%) in the SOC group, the difference being statistically insignificant (*p*=0.0626). 34(49.28%)in favipiravir group had comorbidities , the most common being hypertension 22 (31.88%) followed by diabetes 14 (20.29%) which was significantly more (*p=0.0059*) compared to the SOC group in which 127(31.75%) of the patients had comorbidities the most common being hypertension 104 (26%) followed by diabetes 80(20%).

The median duration of starting treatment from symptom onset 4(2-4) in favipiravir group versus 4 (2-6) in SOC group, the difference being statistically significant (*p=0.0201*).

favipiravir group had 17 (24.64%) patients on O_2 support vs. 49 (12.25%) in SOC group (*p=0.0133*)

Viral Clearance

The patients in both cohorts had their repeat samples tested on day 10 as per institutional protocols. Out of 69 patients in favipiravir group, 65 (94.20%) patients tested negative by RT PCR on the 10th day whereas in the SOC group, 224 (56%)patients out of 400 tested negative by RT PCR on the 10th day (*p<0.0001*).

On further analyzing the data of the favipiravir Group, out of the 34 patients with comorbidities, 24 (70.59%) of them had turned negative by Day 6 and 32 (94.11%) had turned negative by day 10. On comparing with the group with nil comorbidities, 25(71.42%) of the 35 patients had turned negative on day 6 and 33(94.26%) had turned negative by day 10 giving a non-significant *p* value of 1 in both cases. This demonstrates efficacious viral clearance irrespective of comorbidities.

Clinical Outcome

Out of 69 patients in the favipiravir arm, 17 (24.64%) were on oxygen support which reduced to 0 (0%) on day 10, where as in the standard of care group, 49 (12.25%) patients were on oxygen support initially which increased to 54 (13.5%). This difference in the outcome was significant (*p=0.0002).*

Adverse Effects

Out of the 69 patients, 12 (17.39%) patients had developed mild transaminits (Alanine Transaminase <3x Upper Limit of Normal) and 3 (4.35%) patients developed diarrhea. No other adverse events were noted.

Discussion

After 6 & 10 days of treatment with favipiravir, 48 (69.57%) & 65 (94.20%) of the 69 patients tested negative for the virus, respectively. This is comparable to the results published by an ongoing trial study in Russia COVIDFPR 01, which showed 65% & 87.5% of the 40 patients were tested negative for the virus after 4 days & 10 days of treatment with favipiravir, respectively[8].This is important because around 80-85% of COVID-19 patients suffer from mild to moderate disease and enable propagation of the virus[9].

Rates of clinical improvement seen in mild to moderate cases in our study was 71% & 100% on day 6 & day 10, respectively, which is comparable to the Japanese observational study, in which rates of clinical improvement at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5% for mild and moderate, respectively[10].

In our study 15 (21.74%) out of 69 patients developed side effects in the form of transaminitis& diarrhea, which is comparable to the study in Japan, in which adverse reactions were seen in around 20% of the patients who received favipiravir[10.]

Our study has several strengths. First, this study is one of the very few studies carried out in South Asia exploring the effectiveness of favipiravir in active clinical cases of COVID-19. Second, it included a wide range of patients with varying ages, comorbidities and disease severity from mild illnesses to moderate pneumonias requiring O_2 support. Due to meticulous documentation, it was possible for us to evaluate a variety of measures and compare it with a very large historical cohort of a similar set of patients admitted earlier.

Our study has certain limitations as well. First is the small sample size in the favipiravir group (N=69) on a nearly homogenous ethnic population which may not be enough to generalize our findings. Second, there were some differences in the drugs being administered as SOC in both groups, a significant difference being steroids (Methylprednisolone or Dexamethasone). 28 (40.58%) of the patients in favipiravir group were administered steroids as part of the SOC vs 84 (21%) in the SOC only group (*p=0.0011*) which may be a confounding factor. Another limitation was the comparison with a historical cohort, any mutation in the virus strain over the period of a couple of months could have influenced our results.

Conclusion

Our study demonstrates efficacy of favipiravir in mild to moderate COVID-19 pneumonia patients in enhancing viral clearance and clinical improvement demonstrated by wean off from oxygen. Further studies over a larger and more varied population are needed for further evaluation of favipiravir in COVID-19.

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